

## WHAT IS CLAIMED IS:

- Exo A*
1. A method for enhancing the adjuvant effect of IL-12 comprising: co-administering to a mammalian patient said IL-12, a vaccine antigen, and an effective amount of a nitric oxide inhibiting and/or neutralizing agent.
  2. The method according to claim 1 wherein said agent is an agent that inhibits or reduces the synthesis of nitric oxide *in vivo*.
  3. The method according to claim 1 wherein said agent is an agent that breaks down, absorbs, metabolizes or eliminates nitric oxide *in vivo*.
  4. The method according to claim 1 wherein said co-administration comprises simultaneously administering said agent with said IL-12 and said antigen.
  5. The method according to claim 1 wherein said co-administration comprises sequentially administering said agent, said IL-12 and said antigen, in any order.
  6. The method according to claim 3 wherein said co-administration comprises administering said IL-12 before said agent.
  7. The method according to claim 2 wherein said agent inhibiting nitric oxide generation is an inhibitor of nitric oxide synthase.
  8. The method according to claim 7 wherein said agent is specific for inducible nitric oxide synthase.
  9. The method according to claim 2 wherein said agent is selected from the group consisting of L-N<sup>G</sup> monomethyl arginine (L-NMMA), L-N<sup>G</sup>
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nitroarginine (L-NORAG), L- $N^G$  nitroarginine methylester (L-NAME), L- $N^G$  nitroarginine p-nitroanilide (L-NAPNA), L- $N^G$  aminoarginine (L-NAA), L- $N^G$  cyclopropylarginine, L- $N^G$  allylarginine, asymmetric L- $N^G N^G$  dimethylarginine (L-ADMA), L- $N^w$ iminoethyl ornithine (L-NIO), 7-nitro indazole (7-NI), 2,7 dinitro indazole, 3-bromo 7-nitro indazole, aminoguanidine, N,N'-diaminoguanidine, dimethylguanidine, diphenyleneiodonium, iodoniumdiphenyl, di-2-thienyliodonium, chlorpromazine, trifluoperazine, pimozide, clozapine, calmidazolium, 2,4 diamino-6-hydroxypyrimidine, methotrexate, N-acetyl-5-hydroxytryptamine, miconazole, ketoconazole, clotrimazole, imidazole, 1-, 2- and 4-phenylimidazole, methylene blue, NO, carbon monoxide, ebselen, phencyclidine, and antineoplastic agents (doxorubicin, aclarubicin).

10. The method according to claim 9 wherein said agent is L-NAME.

11. The method according to claim 9 wherein said agent is L-NMMA.

12. The method according to claim 3 wherein said agent is a nitric oxide scavenger.

13. The method according to claim 12 wherein said scavenger is selected from the group consisting of N-acetyl cysteine, pyrrolidine dithiocarbamate, and hemoglobin.

14. The method according to claim 1 wherein said vaccine antigen is a mammalian tumor cell antigen.

15. The method according to claim 1 wherein said vaccine antigen is a pathogenic antigen selected from the group consisting of bacterial antigens, viral antigens, and parasitic antigens.

16. A method for reducing the immunosuppressive effects of IL-12 treatment comprising: co-administering with said IL-12, an effective amount of a nitric oxide inhibiting and/or neutralizing agent.

17. The method according to claim 16 wherein said co-administration comprises simultaneously administering said agent with said IL-12.

18. The method according to claim 16 wherein said co-administration comprises sequentially administering said agent, and said IL-12.

19. The method according to claim 18 wherein said co-administration comprises administering said IL-12 before said agent.

20. The method according to claim 16 wherein said agent is an inhibitor of nitric oxide generation is an inhibitor of nitric oxide synthase.

21. The method according to claim 20 wherein said agent is specific for inducible nitric oxide synthase.

22. The method according to claim 20 wherein said inhibitor is selected from the group consisting of L-N<sup>G</sup> monomethyl arginine (L-NMMA), L-N<sup>G</sup> nitroarginine (L-NORAG), L-N<sup>G</sup> nitroarginine methylester (L-NAME), L-N<sup>G</sup> nitroarginine p-nitroanilide (L-NAPNA), L-N<sup>G</sup> aminoarginine (L-NAA), L-N<sup>G</sup> cyclopropylarginine, L-N<sup>G</sup> allylarginine, asymmetric L-N<sup>G</sup>N<sup>G</sup> dimethylarginine (L-ADMA), L-N<sup>w</sup>iminoethyl ornithine (L-NIO), 7-nitro indazole (7-NI), 2,7 dinitro indazole, 3-bromo 7-nitro indazole, aminoguanidine, N,N'-diaminoguanidine,

dimethylguanidine, diphenyleneiodonium, iodoniumdiphenyl, di-2-thienyliodonium, chlorpromazine, trifluoperazine, pimozide, clozapine, calmidazolium, 2,4 diamino-6-hydroxypyrimidine, methotrexate, N-acetyl-5-hydroxytryptamine, miconazole, ketoconazole, clotrimazole, imidazole, 1-, 2- and 4-phenylimidazole, methylene blue, NO, carbon monoxide, ebselen, phencyclidine, and antineoplastic agents (doxorubicin, aclarubicin).

23. The method according to claim 22 wherein said agent is L-NAME.

24. The method according to claim 22 wherein said agent is L-NMMA.

25. The method according to claim 16 wherein said agent is a nitric oxide scavenger.

26. The method according to claim 25 wherein said scavenger is selected from the group consisting of N-acetyl cysteine, pyrrolidine dithiocarbamate, and hemoglobin.

27. A method for reducing the toxicity of IL-12 treatment comprising: co-administering with an effective dose of said IL-12, an effective amount of a nitric oxide inhibiting and reducing agent.

28. The method according to claim 27 wherein said co-administration comprises simultaneously administering said agent with said IL-12.

29. The method according to claim 27 wherein said co-administration comprises sequentially administering said agent, and said IL-12.

30. The method according to claim 27 wherein said co-administration comprises administering said IL-12 before said agent.

31. The method according to claim 27 wherein said effective amount of IL-12 is a low dose thereof.

32. The method according to claim 27 wherein said agent is an inhibitor of nitric oxide synthase.

33. The method according to claim 32 wherein said agent is specific for inducible nitric oxide synthase.

34. The method according to claim 32 wherein said inhibitor is selected from the group consisting of L-<sup>N<sup>G</sup></sup> monomethyl arginine (L-NMMA), L-<sup>N<sup>G</sup></sup> nitroarginine (L-NORAG), L-<sup>N<sup>G</sup></sup> nitroarginine methylester (L-NAME), L-<sup>N<sup>G</sup></sup> nitroarginine p-nitroanilide (L-NAPNA), L-<sup>N<sup>G</sup></sup> aminoarginine (L-NAA), L-<sup>N<sup>G</sup></sup> cyclopropylarginine, L-<sup>N<sup>G</sup></sup> allylarginine, asymmetric L-<sup>N<sup>G</sup></sup><sup>N<sup>G</sup></sup> dimethylarginine (L-ADMA), L-<sup>N<sup>ω</sup></sup>iminoethyl ornithine (L-NIO), 7-nitro indazole (7-NI), 2,7 dinitro indazole, 3-bromo 7-nitro indazole, aminoguanidine, N,N'-diaminoguanidine, dimethylguanidine, diphenyleneiodonium, iodoniumdiphenyl, di-2-thienyliodonium, chlorpromazine, trifluoperazine, pimozide, clozapine, calmidazolium, 2,4 diamino-6-hydroxypyrimidine, methotrexate, N-acetyl-5-hydroxytryptamine, miconazole, ketoconazole, clotrimazole, imidazole, 1-, 2- and 4-phenylimidazole, methylene blue, NO, carbon monoxide, ebselen, phencyclidine, and antineoplastic agents (doxorubicin, aclarubicin).

35. The method according to claim 34 wherein said agent is L-NAME.

36. The method according to claim 34 wherein said agent is L-NMMA.
37. The method according to claim 27 wherein said agent is a nitric oxide scavenger.
38. The method according to claim 37 wherein said scavenger is selected from the group consisting of N-acetyl cysteine, pyrrolidine dithiocarbamate, and hemoglobin.
39. A therapeutic composition comprising IL-12, characterized by reduced toxicity in mammals, said composition comprising an effective dose of said IL-12 and an effective amount of a nitric acid inhibiting and/or neutralizing agent in a pharmaceutically acceptable carrier.
40. An adjuvant composition suitable for use with a vaccine antigen comprising an effective adjuvanting amount of IL-12 and an effective amount of a nitric oxide inhibiting and/or neutralizing agent in a pharmaceutically acceptable carrier.
41. A vaccine composition comprising an effective adjuvanting amount of IL-12, an effective amount of a nitric oxide inhibiting and/or neutralizing agent, and an effective protective amount of a vaccine antigen in a pharmaceutically acceptable carrier.

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